Claim 37: at page 4, first full paragraph.

Claims 64-65: at page 5, first full paragraph.

Claim 66: at pages 6-7.

Claims 67-69: these correspond to original claims 33, 34 and 38.

Claims 70-71: at page 5, first full paragraph.

II. Amendments to the Specification

The specification has been amended to insert section headings and correct typographical errors. The first two full paragraphs on page 3 are deleted because these are redundant with paragraphs on page 2. The section of the specification on page 11 describing the figures has been moved to a point earlier in the application in accordance with the order set forth in the MPEP 608.01(a).

III. Information Disclosure Statement

The Examiner objects to the information disclosure statement filed March 29, 2000, because it does not include a concise explanation of the relevance of those references that are not in the English language. Specifically, the Examiner says that references AC-AL have not been considered.

As an initial matter, Applicants note that reference AC is in English and that the checked off copy of the March 29th information disclosure statement shows that the Examiner has considered this reference. Applicants also note that they addressed this issue by filing a supplemental information disclosure statement on August 8, 2001, which provided English language patents or publications that correspond to references AB, and AD-AL in the March 29th information disclosure statement. An English translation of reference AN was also provided. The checked off copy of the August 8th information disclosure statement provided with the Office Action shows that the Examiner has considered all of these references.

IV. Presently Claimed Invention

The nomenclature regarding the various forms of vWF is somewhat complicated. To provide clarification and a better understanding of the currently claimed invention, copies of pages 77 and 78 from an article by Eikenboom, et al. (Haemophilia 1:77-90, 1995; referred to in the specification at page 1, paragraph 3 and provided as reference AR in the information disclosure statement filed March 9, 2000) including a few clarifying handwritten notes are attached hereto as Appendix A. The text in the section entitled "Gene and biosynthesis of vWF" and Figure 1 provide a summary of the processing of the vWF protein.

As can be seen in these attachments and as described on page 1, vWF is synthesized as a single-chain molecule precursor protein of 2813 amino acid residues (referred to in the application as "*prepro-vWF*"). As illustrated in Figure 1 of Appendix A, the prepro form of vWF includes a 22 amino acid long signal peptide, a 741 amino acid long propeptide segment, and a 2050 amino acid long segment constituting the mature vWF protein. During post-translational modification, the 22 amino acid signal peptide is removed from the prepro vWF to generate a segment that includes the propeptide and mature vWF segments (referred to in the application and the article as "*pro-vWF*"). Pro-vWF dimerizes via the formation of disulfide bridges to form pro-vWF dimers. These dimers are subsequently assembled into multimers of high molecular weight by the formation of disulfide bonds between the dimers. During the dimerization process, the 741 amino acid propeptide segment (variously referred to in the application, for example, as the "*vWF-propeptide,*" "*propeptide of vWF,*" the "*propolypeptide*" or simply as "*pp-vWF*") is cleaved off, thus leaving the 2050 amino acid long mature vWF protein.

Thus, the vWF propeptide of the preparation described in claim 31 refers to the vWF propeptide segment that is removed from pro-vWF. Certain preparations can also include additional components, such as a hemostasis protein (e.g., factor VIII and mature vWF), a platelet component or a phospholipid, for example. Still other preparations (e.g., as set forth in claim 67) comprise pro-vWF, a protein that includes the vWF propeptide (see Figure 1 of Appendix A).

V. Objections

As requested by the Examiner, independent claim 31 has been amended to indicate that the abbreviation vWF is an acronym for von Willebrand Factor.

Claim 44 is objected to as being a substantial duplicate of claim 34 (now claim 68). Applicants respectfully disagree, as claim 68 is drawn to a preparation that comprises recombinant pro-vWF, whereas claim 44 is drawn to recombinant vWF propeptide. As discussed in the preceding section, pro-vWF and vWF propeptide refer to different proteins. In particular, pro-vWF refers to a protein that includes the vWF propeptide segment *plus* the mature vWF segment. In view of these differences, the language of claims 33 (now 67), 34 (now 68) and 38 (now 69) is appropriate.

VI. Claim Rejections under 35 U.S.C. 112

Claim 32 is said to be indefinite for use of the term "consisting essentially of". Applicants respectfully disagree with this rejection because, as the Examiner acknowledges, the phrase is an accepted transitional phrase whose meaning and scope have been established by the courts (see, e.g., MPEP 2111.03). Contrary to the assertion in the Office Action, applicants are not required to specify what unrecited additional components are intended to be excluded from the scope of the claim. Rather, Applicant only need demonstrate that a component(s) in a cited prior art reference is excluded from the scope of the claims in response to a rejection based on the cited reference (see, e.g., MPEP 2111.03). The Examiner is also referred to page 5, the first full paragraph, which provides a description of the composition of certain such preparations that are encompassed by claim 32 (the preparation are not necessarily limited to such compositions, however). Applicants also note that claim 32 is a proper dependent claim because, as noted by the Examiner, the transitional phrase "consisting essentially of" is narrower in scope than the transitional phrase "comprising", which is used in claim 31.

Claims 33, 34 and 38 (now 67-69, respectively) are rejected as being indefinite because the phrase "pro-vWF" is said to be synonymous with the phrase "vWF

propeptide." As discussed supra, this is not the case. Rather, pro-vWF refers to a protein that includes vWF propeptide *and* the mature vWF subunit (see Figure 1 of Appendix A).

Claim 37 has been amended as requested by the Examiner to clarify that FEIB activity means factor VIII inhibitor bypassing activity, which phrase is defined, for example, at page 4, lines 13-15.

VII. Claim Rejections under 35 U.S.C. 102

A. Burnouf-Radosevich et al.

Claims 31-33, 35-40 and 43-44 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Burnouf-Radosevich et al. ("Burnouf") (U.S. Patent 5,408,039). For the reasons that follow, Applicants respectfully disagree.

To show that a claim is anticipated, it must be shown that "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." (MPEP 2131 and Verdegaal Bros. v Union Oil Co. of California, 814 F.2d 628. 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). Burnouf, however, is completely silent regarding preparations containing vWF propeptide or pro-vWF as set forth in the currently claimed invention. Instead, the discussion in Burnouf is limited to chromatographic methods for preparing a vWF concentrate for therapeutic use. The vWF composition produced is "characterized by a high content in high molecular weight multimers" (col. 3, lines 8-9; emphasis added). Thus, the preparations obtained according to the methods discussed in Burnouf are limited to those containing mature vWF, as this is the subunit of vWF that is multimeric (see discussion supra and the Eikenboom article in Appendix A).

The Office Action hypothesizes, however, that because of incomplete proteolysis of pro-vWF that the partially purified solution discussed in Burnouf (col. 5, lines 55-60) contains a mixture of cleaved vWF (i.e., mature vWF) and uncleaved vWF (which the Office Action refers to as the propolypeptide), which mixture also has been treated for viral inactivation. It appears from this statement that there is confusion regarding the meaning of "propolypeptide." As pointed out supra in the description of

the invention, the propolypeptide is the subunit that is cleaved from pro-vWF to yield mature vWF. Thus, it appears that the Examiner is arguing that as a result of incomplete proteolytic cleavage that the solution might contain a mixture of pro-vWF and mature vWF. Taken to its full conclusion, presumably such an argument also means that the cryoprecipitate further contains propolypeptide (i.e., vWF propeptide).

Hence, it appears that the Examiner is arguing that the "Factor VIII/vWF mixture" inherently contains pro-vWF and/or vWF propeptide due to incomplete proteolysis of pro-vWF. To reject a claim as being anticipated under the inherency doctrine, the Patent Office must overcome a substantial burden. Specifically, the Federal Circuit has said:

> To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' (MPEP 2112; citing In re Robinson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-1951 (Fed. Cir. 1999) (emphasis added).

Applicants submit that the rationale set forth in the Office Action fails to show that vWF propeptide is necessarily present in the compositions discussed in Burnouf; consequently, Burnouf fails to anticipate the claimed invention. First, the alleged anticipating composition to which the Examiner refers is one prepared from a cryoprecipitate formed from plasma (see col. 5, lines 29-48). Applicants point out that vWF molecules in such a source material do not contain vWF propeptide because the propetide subunit is cleaved from the multimeric form of vWF before it is released from

intracellular storage sites into the circulation (see, e.g., page 56, lines 4-5 of article by Fishcer et al. (Thrombosis Research 84:55-56, 1996) attached hereto as Appendix B, as well as articles cited therein). Secondly, even if, arguendo, one agreed that pro vWF was present in the initial plasma and underwent partial proteolysis as proposed in the Office Action, no evidence is presented to support the view that pro-vWF or vWF propeptide would remain in solution following the centrifugation and aluminum hydroxide purification steps which precede formation of the composition to which the Examiner points (see col. 5, lines 40-48). Thus, at best, the inherency rationale set forth in the Office Action simply sets forth probabilities or possibilities for the existence of vWF propeptide or pro-vWF in the composition; as set forth above, however, such a showing is insufficient under the law.

In view of the foregoing evidence and reasons, it is submitted that the anticipation rejection based on Burnouf should be withdrawn.

B. Rejection Based on Takagi et al.

Claims 31-33, 39-40 and 43-44 are said to be anticipated by Takagi et al. ("Takagi") (J. Biol. Chem. 264:6017-6020, 1989). For the reasons that follow, Applicants respectfully disagree.

As noted in the preceding section, a claim is not anticipated unless it is shown that the cited reference describes each element of the claimed invention. While Takagi discusses certain methods and compositions that contain vWF propeptide, as the Examiner acknowledges on page 9 of the Office Action, Takagi fails to describe a pharmaceutical preparation comprising vWF propeptide that has been "treated for at least one of virus inactivation and virus recovery" (see claims 31 and 67).

Since the Examiner has not shown that Takagi describes each element of the presently claimed invention, the anticipation rejection based on this reference should be withdrawn.

VIII. Claim Rejections under 35 U.S.C. 103

A. Rejection based on Leyte et al., Takagi and Burnouf-Radosevich

Claims 31-40, and 43-44 are rejected as allegedly being obvious over Leyte et al ("Leyte") (Biochem. J. (1991) 274:257-261) and Takagi and Burnouf. For the reasons that follow, Applicants respectfully disagree.

1. Leyte Reference

Leyte discusses binding experiments that were conducted with two different types of mature vWF, the different types having identical amino acid sequences but differing in the process by which they were generated and thus in the extent of multimerization. One mature vWF protein (what Leyte refers to as flvWF) was expressed in cells transformed with a plasmid containing the "full length vWF cDNA" (see, p. 258, section entitled "Plasmid Constructions). Applicants understand this to mean that the plasmid encoded pre-pro-vWF (see Figure 1 of Appendix A). During post-translational processing in the transfected cell, the pre- and pro-sequences are removed, thus yielding mature vWF (see, e.g., p. 259, col. 1, 3rd sentence in the section entitled "Expression of recombinant vWF in AtT-20 cells"). The other mature vWF protein (what Leyte refers to as vWFdelpro) was expressed in cells transformed with a plasmid containing the full length vWF cDNA, but without the segment encoding the propolypeptide, i.e., a cDNA encoding just the pre-vWF and mature vWF subunits. During post-translational processing in cells transfected with this construct, the pre-sequence is cleaved away, thus leaving mature vWF.

Leyte conducted binding experiments and found that while flvWF bound Factor VIII, vWFdelpro did not. Thus, the experiments showed that two proteins that have identical amino acid sequences (following complete post-translational processing) nonetheless exhibit differences in their ability to bind Factor VIII. Leyte attributes this peculiar finding to the role that the propolypeptide (i.e., vWF propeptide) plays during processing of prepro vWF. In particular, the authors theorize that as a component of the immature protein, the propolypeptide segment plays some kind of role in the disulfide

bond formation during processing of pre-pro vWF to mature vWF, particularly in the region of mature vWF that binds Factor VIII.

All the binding experiments discussed in Leyte, however, are limited to mature vWF produced via these two different methods. No experiments were conducted with vWF propeptide (i.e., the propolypeptide) itself, or pro-vWF.

2. No Motivation to Combine the Cited References

The Examiner takes the position that it would have been obvious to make a composition comprising vWF propolypeptide (i.e., vWF propeptide) as taught by Leyte and Takagi and to treat the composition for virus inactivation or removal as discussed by Burnouf. According to the Examiner, one of ordinary skill would be motivated to combine the teachings of these references because vWF compositions are routinely used in methods of treatment and because Leyte discusses a potential role for vWF propeptide in formation of a functional Factor VIII binding site on mature vWF, complex formation between these two proteins being important in maintenance of haemostasis. One would also be motivated to combine the viral inactivation procedure discussed in Burnouf to make a safer composition.

As an initial matter, it is noted that contrary to the foregoing assertion Leyte does not discuss compositions that contain vWF propeptide. As noted above, the discussion in Leyte is limited to methods for recombinantly producing pre-pro-vWF or vWF *without* vWF propeptide. Experiments are conducted with mature vWF produced after processing of these proteins. Leyte contains no discussion whatsoever regarding vWF propeptide per se.

To show motivation evidence must be provided that would "impel one skilled in the art to do what the patent applicant has done." (MPEP 2144; and Ex parte Levengood 28 USPQ2d 1300, 1302 (Bd. Pat. App. and Inter. 1993) (emphasis added). The rationale presented in the Office Action based on the discussion in Leyte falls far short of a rationale that would impel one of ordinary skill to make the combination that is proposed. First, it is important to recognize that the activity Leyte suggests for vWF

propeptide is an activity ascribed to the vWF propeptide segment during post-translational processing of pre-pro vWF. There is no discussion in Leyte regarding the activity of vWF propeptide per se, i.e., the vWF propeptide itself, rather than as a component of the larger immature vWF. Secondly, even Leyte notes that the potential role ascribed to vWF propeptide is simply a proposal (see final sentence).

Thus, the motivation proposed in the Office Action based on the discussion in Leyte is at best an obvious to try rationale. The courts have been clear that a rationale based on evidence simply that an approach holds promise or a rationale based on general guidance as to the particular form of the claimed invention is not sufficient to establish motivation (see, e.g., MPEP 2145).

Takagi also fails to provide the requisite motivation to combine the cited references. As Applicants previously pointed out in their response to the restriction requirement, any discussion in Takagi of a pharmaceutical utility for vWF propeptide (what Takagi refers to as the propolypeptide) is speculative at best. Based on the studies conducted, Takagi is only willing to theorize that there is a "possibility" of a physiological role for vWF propeptide (see, e.g., p. 6017, second column, last sentence before the section entitled "Experimental Procedures"; p. 6018, second column, second sentence of first full paragraph; and p. 6019, the penultimate sentence) (emphasis added).

Burnouf lacks the requisite motivation because it is completely silent regarding vWF propeptide.

In view of the fact that none of the cited references provide a motivation that would impel one skilled in the art to make the preparations of the currently claimed invention, Applicants respectfully request that this obviousness rejection be withdrawn.

3. No Expectation of Success

Even if one combined the cited references as proposed in the Office Action, the present claims would not be rendered obvious because there would be no reasonable expectation that a preparation comprising vWF propeptide would be effective in treating blood coagulation disorders. Considering Leyte first, one of ordinary skill in

the art could not reasonably conclude that an apparent activity of vWF propeptide as a component of pre-pro-vWF during post-translational processing would be retained by vWF propeptide alone, or by the propolypeptide as a component of pro-vWF.

Turning to Takagi, as noted in the preceding section, all discussion of a biological activity for vWF propolypeptide is characterized simply as being a "possibility." Thus, based upon the speculation in Takagi, one of ordinary skill in the art could not reasonably conclude that the propolypeptide would have activity in treating blood coagulation disorders.

Thus, for these reasons also, the obviousness rejection based on Burnouf, Takagi and Leyte should be withdrawn.

B. Rejection based on Leyte, Takagi, Burnouf and Kaufman

Claim 41 stands rejected as allegedly being obvious over Leyte, Takagi and Burnouf in view of Kaufman (U.S. Patent 5,198,349). For the reasons that follow, Applicants respectfully disagree.

Kaufman is cited simply for the proposition that it would be obvious to utilize phospholipids to stabilize preparations containing vWF propeptide. However, Kaufman is completely silent about vWF propeptide, and particularly vWF propeptide in combination with phospholipids. Instead, Kaufman discusses how certain components such as phospholipids and vWF can be utilized to stabilize Factor VIII. The fact that phospholipids are useful to stabilize Factor VIII provides no motivation to utilize phosopholipids with the completely different proteins, vWF propeptide or pro-vWF. Further, one of ordinary skill could not reasonably expect that simply because phospholipids have a stabilizing effect on Factor VIII that it would exhibit a similar effect with vWF propeptide or pro-vWF.

Thus, because the cited references collectively fail to provide the requisite motivation to combine the reference to obtain the claimed invention and fail to provide an expectation that vWF propeptide or pro-vWF containing the vWF propeptide would be

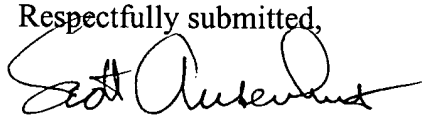
useful in treating blood coagulation disorders, the obviousness rejection based on the foregoing references should be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 303-571-4000.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The first paragraph on page 1, has been amended as follows:

FIELD OF THE INVENTION

The invention relates to a pharmaceutical preparation comprising the vWF-propeptide (pp-vWF).

The second paragraph on page 1, has been amended as follows:

BACKGROUND OF THE INVENTION

Von Willebrand factor (vWF) is a glycoprotein circulating in plasma as a series of ~~mulitimeres~~ multimers ranging in size from about 500 to 20,000 kD. Multimeric forms of vWF are composed of 250 kD polypeptide subunits linked together by disulfide bonds. vWF mediates the initial platelet adhesion to the sub-endothelium of the damaged vessel wall, only the larger multimers also exhibiting hemostatic activity. It is assumed that endothelial cells secret large polymeric forms of vWF and that those forms of vWF which have a low molecular weight (low molecular weight vWF) have arisen from proteolytic cleavage. The multimers having large molecular masses are stored in the Weibel-Pallade bodies of the endothelial cells and liberated upon stimulation.

The third full paragraph on page 3, has been amended as follows:

SUMMARY OF THE INVENTION

It is the object of the present invention to provide a vWF pharmaceutic with improved properties. The preparation should enhance the intrinsic blood coagulation activity in individuals and reduce the arterial thrombotic risk of vWF therapy.

The final paragraph beginning on page 3, has been amended as follows:

The object is solved by the present invention by providing a pharmaceutical preparation for treating blood coagulation disorders comprising an effective amount of vWF propeptide. It was found out that pp-vWF plays an essential role in blood coagulation. It promotes the intrinsic blood coagulation and thereby acts on secondary ~~heostasis~~ hemostasis. At the same time it inhibits the platelet adhesion and controls the primary hemostatic activity of mature vWF by binding to collagen. Based on these findings, a vWF preparation can be improved providing additional pro-vWF or pp-vWF as a separate effective protein in the vWF preparation. pp-vWF controls the primary hemostatic activity of the mature vWF and thus reduces the potential thrombotic risk of ~~vWF~~ vWF, for ~~e.g.~~ example inducing arterial thrombosis as indicated by the prior art.

The final paragraph beginning on page 9, has been amended as follows:

Yet another aspect of the present invention is the use of pp-vWF and/or pro-vWF containing the pp-vWF for the preparation of a pharmaceutical composition for treating a patient at a risk of blood coagulation disorders, such as vWD, hemophilia (~~f.e.~~ e.g. phenotypic hemophilia, hemophilia A and factor VIII inhibitors).

The first full paragraph on page 10, has been amended as follows:

The effective dosage of the preparation when applied will vary depending on the respective ~~syndrom~~ syndrome and preferably should be chosen after determination of the blood levels of the critical blood factors or risk for thrombosis in the patient. The optimum dosage also depends on whether or not the parenteral, preferably intravenous, subcutaneous or intramuscular ~~adiministration~~ administration is to be effected in bolus form or as a depot. By using a suitable carrier material such as liposomes a peroral administration is feasible. It also depends on whether it is to be applied systemically and/or locally at the site of the blood coagulation disorder.

The final paragraph on page 13, has been amended as follows:

Thrombin potential increased in parallel with the increase of propeptide after the treatment with a recombinant ~~provWF~~ pro-vWF preparation. ELISA results showed, that a few percent of pro-vWF remained in the circulation after 15 minutes, and it could no longer be detected (data not shown), but a significant increase in the propeptide and vWF was observed. In contrast, no propeptide and also no substantial thrombin potential was observed in the dog after the plasma derived vWF infusion, despite ~~of~~ the vWF antigen level increase.

IN THE CLAIMS:

Claim 31 has been amended as follows:

31. (Twice amended) A pharmaceutical preparation for treating blood coagulation disorders, said preparation comprising ~~an effective amount of vWF~~ von Willebrand Factor (vWF) propeptide and having been treated for at least one of virus inactivation and virus removal.

Claim 37 has been amended as follows:

37. (Once amended) A preparation as set forth in claim 36, wherein said blood factor is selected from the group consisting of mature vWF, factor VIII, activated blood coagulation factors, and blood factors with factor VIII inhibitor bypassing activity ~~and FEIB activity and FEIBA~~.

Claim 41 has been amended as follows:

41. (Once amended) A preparation as set forth in claim 31, further comprising a phospholipids.